UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

09/149,718 09/08/98 GAMES K ANS-101-CIP(

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

HM12/0129

PATREA L PABST
ARNALL GOLDEN & GREGORY
2700 ONE ATLANTIC CENTER
1201 W PEACHTREE STREET
ATLANTA GA 30309-3450

CROUCH, D
EXAMINER

1632
ART UNIT | PAPER NUMBER

01/29/01
DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/149,718	Games et al.
Examiner	**Group Art Unit**
Deborah Crouch	1632

☒ Responsive to communication(s) filed on *Oct 30, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20, 22-26, and 28-58* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20, 22-26, and 28-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Applicant's arguments filed October 30, 2000 in paper no. 10 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-20,22-26 and 28-58 are pending.

It is noted that the claims in the appendix are not the claims of record. The claims in the preliminary amendment filed September 8, 1998 are those currently under examination. A review of the file has not established any other preliminary amendment.

Applicant's extensive use of footnotes is confusing as to whether they constitute parenthetical information or actual arguments to the examiner's previous rejections. Any rebuttal, evidence or argument that applicant wants the examiner to consider should be in the body of the response and not in footnotes.

There appears to be several applications to related subject matter with same assignee. Applicant is requested to indicate in the response to this office action any other applications so related.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20,22-26 and 28-58 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7,9-16 and 18-27 of copending Application No. 09/149,856 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '856 are obvious over each other.

This is a provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Applicant states that they will consider filing a terminal disclaimer once allowable subject matter has been indicated.

Claims 1-20,22,23,26,29-50,53,54,57 and 58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,811,633 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-20,22,23,36,29-50,53,54,57 and 58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,720,936 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56-58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '486 are obvious over each other.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56-58 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 10-12 of U.S. Patent No. 5,604,102 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Applicant argues, with regard to US Patents 5,811,633, 5,720,936, 5,612,486 and 5,604,102 do not recite expression levels of Aβ-related expression production as required by the claims. Applicant's argue that prior to applicant's discovery, it was not known that the high expression levels of Aβ-related expression products in transgenic mice is related to the development of plaques closely related to those found in Alzheimer's Disease. Applicant argues that the inherency reasoning of the examiner in the previous office action is incorrect and improper. Applicant argues that there is no evidence that the mice of US Patents 5,811,633, 5,720,936, 5,612,486 and 5,604,102 expressed any Aβ-related expression products at the claimed phenotypic level. Applicant argues that in particular the patents do not teach that the mice develop plaques that stain with Congo red. Applicant argues that at best the claimed expression levels

would be at best be present in only a subset of the mammals claimed in the cited patents, and that applicant's discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. These arguments are not persuasive.

The lack of recognition that a product, in this case the transgenic mouse of the patents, has a particular phenotype, in the instant case staining with Congo red or a particular expression level phenotype, does not remove the inherency of the phenotypes. The mice of the patents can not structurally be distinguished from those being claimed, as the particular APP transgenes of the patented mice, or patented methods of using mice containing particular APP transgenes are encompassed within the claim. If the structure of the patented mice or the structure of mice used in patented methods of assay are the same, or are encompassed by the claims, inherency is present. A product an its properties can not be separated. A new patent, with a new enforcement term can not issue because someone found a previously unrecognized characteristic or phenotype, such as the argued Congo red staining or Aβ peptide or related proteins expression level.

Claims 1-20,22,23,26,29-50,53,54,57 and 58 are directed to an invention not patentably distinct from claims 1-6 of commonly assigned 5,811,633. Specifically, instant claims 1-20,22,23,26,29-50,53 and 54 are drawn to a method of assay using a mouse of the same scope as the mouse of claims 1-6 pf '633. Since a product and its properties can not be separated, the mice of the instant assay would inherently encompass the mice of '633. Further the mice of '633 are defined to be an assay for Alzheimer's Diseases therapeutics. Thus there is no patentable distinct between the instant claims and those of '633.

Claims 1-20,22,23,26,29-50,53,54,57 and 58 are directed to an invention not patentably distinct from claims 1-6 of commonly assigned U.S. Patent 5,720,936. Specifically, instant claims 1-20,22,23,26,29-50,53 and 54 and claims 1-6 pf '936 are both drawn to methods of assay using mice that are of the same scope. The mice of the instant assay comprise the same transgene construct as the transgene construct of '936. Since a product and its properties can not be separated, the instant assay would inherently encompass the assay of '936. Thus there is no patentable distinct between the instant claims and those of '936

Commonly assigned U.S. Patent 5,811,633 and U.S. Patent 5,720,936, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

At pages 33-34 of the response filed October 30, 2000, applicant's state that Samuel Wadsworth, Benjamin Snyder, Cha-mer Wei and Paul Liebowitz are prior inventor of subject matter 5,811,633 and 5,70,936. Thus, the application is not abandoned. However, there is no statement by the assignee that the inventions were commonly owned at the time the invention in this application was made. A review of assignment records at the PTO indicates that the instant invention was assigned to Athena Neurosciences at the time of filing 6/5/95 via the priority document, while US Patents 5,811,633 and 5,720,936 were assigned to TSI Corporation on 6/5/95. These patents therefore qualify as art under 35 USC 102(f).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,2,5-7,9,11,13,15-20,24-26,28-30,33,34,36,38,40 and 42-48,51-53 and 56-58 remain rejected under 35 U.S.C. 102(a) as being clearly anticipated by WO 95/11968 for reasons of record. '968

teaches a method for identifying drugs effective in the treatment of Alzheimer's Disease wherein the assay comprising administering drugs of interest to transgenic non-human mammals that express the Swedish mutation APP operatively linked to the rat NSE promoter (page 39-40, bridg. parag.; page 41, lines 16-22 and page 42, lines 17-24). As the construct disclosed in '986 is also claimed by applicant, the expression levels, characteristics and features claimed for the mouse of the instant assay are an inherent feature of the mouse of the assay in '968.

Applicant argues that the examiner's use of inherency is incorrect and thus improper. Applicant argues that a claim is not inherent unless extrinsic evidence clearly shows the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Applicant argues that WO 95/11968 discloses transgenic mice having the Swedish mutation, but not that the mice meet the expression phenotype of the claim. Applicant argues that where a cited reference is silent about the asserted inherent characteristic, evidence must be presented to shown that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. Applicant argues that the claimed expression levels are not a part of the common knowledge of those of skill in the art and are not the kind of thing that would be recognized by those of skill in the art as an understood feature of the mice. Applicant argues there is no evidence that all of the mice of WO 95/11968 will express the transgene, and that at least some of the mice will fail to express the transgene due to as an example insertion side effects. Applicant argues that because of this not all of the mice of WO 95/11968 will have the required expression makes the inherency argument impossible. Applicant argues that in *Glaxo v. Novapharm*, 52 F.3d 1043 (Fed. Cir. 1995, held that an inconsistent result precluded inherency. Applicant also argues that because some mice having the claimed construct may not have the claimed expression, and thus inherency is precluded. Applicant argues that some of the mice disclosed in WO 95/11968 will not necessarily exhibit the claimed expression, even if some of the mice produced would happen to exhibit the claimed expression levels. Applicant argues that the lower rate of success at producing mice having the presently claimed expression

levels, even if it occurred, does not rise to the level of inevitable appearance of the features at issue as required for inherency. These arguments are not persuasive.

The claims of WO 95/11968 meet the structural requirement of the involved instant claims, and as such the expression phenotype would be expected to ensue by the ordinary artisan. Applicant has not offered any arguments or evidence that the mice disclosed in WO 95/11968 would not achieve the claimed phenotypes. In deed the ordinary artisan would have fully expected a transgenic mouse of identical structure to achieve the phenotype, and the recognition of such a phenotype after publication of WO 95/11968 by applicant does not give applicant rights to claiming the same method using the same mouse. The conditions set forth in Finnigan are met. There is no probability or possibility present. The method disclosed in WO 95/11968 uses the same mouse claimed, that is one that falls within the scope of the instant claims. Thus, that mouse would be expected to achieve the claimed phenotypes. Further, applicant has not established that the rate of mice not achieving the claimed phenotype would be so inconsistent that inherency would have been precluded. There is no evidence that the mice of WO 95/11968 would not have necessarily expressed the Aβ protein to the claimed levels. The facts are that the mouse of WO 95/11968 is encompassed by applicant's claims, and thus would very reasonably have had the claimed phenotype. A new feature recognized to an old product does not provide patentability to the old product. Applicant is advised that if the mice of WO 95/11968 do not have the phenotype claimed, and thus do not anticipate claimed method, then serious enablement questions are raised as to the breadth of enablement of applicant's invention.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7,9,11,13,15-20,22,23,26,29-34,36,38,40,42-50,53,54,57 and 58 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by WO 93/14200 for reasons of record. '200 teaches a method of screening for compounds effective in the treatment of Alzheimer's Disease wherein the treatment assay comprises transgenic mice or transformed cells that express a transgene encoding APP770, APP751, APP695, APP770 with FAD mutations at amino acid 717 operably linked to the PDGFβ promoter (page 14,

parag. 1, page 15, parag. 1, page 16, parag. 1, pages 18, parag. 1, lines 4-5 and pages 28-30). The construct disclosed in '200 is the same as that claimed by applicant, and as such the expression levels, characteristics and features of the mouse of the assay claimed by applicant are an inherent feature of the mouse testing model disclosed in '200.

Applicant argues that the transgenic mouse disclosed in WO 93/14200 that produces expression products at the claimed levels, that is having a cDNA/genomic DNA APP construct, is specifically excluded from the claims. This argument is not persuasive. The only claims that exclude the cDNA/genomic DNA APP construct is excluded in claims 28 and 56. Applicant should refer to the amendment filed September 8, 1998. It noted that the claims in the appendix to the response of October 30, 2000 contain such a limitation. However, these are not the claims of record. If such a limitation enters the file, of course, the rejection will need to be reconsidered.

Applicant argues that where a reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. Applicant argues that their arguments regarding inherency in the rejection over WO 95/11968 apply equally to the rejection over WO 93/14200. These arguments are not persuasive.

The examiner's rebuttal to applicant's arguments regarding WO 95/11968 are equally applicable in this instance. In summary, the mouse disclosed in WO 93/14200 is structurally the same as the mouse of the instant claims. Thus it would be expected by the ordinary artisan that the mouse of WO 93/14200 would achieve the same expression levels as the mouse of the claims. Applicant has provided neither evidence or arguments as to why the mice of WO 93/14200 would not be expected to reach the claimed expression levels. There is no requirement that extrinsic evidence be supplied for inherency, especially when the structural feature of the prior art are encompassed by the claimed invention. If the mice of the prior art contain the same transgene as that claimed, then the physical properties of the prior art mice are inherently those of the claimed mice. The recognition of new physical properties of an old product does

not make the old product patentable. Thus, the claimed method is anticipated by the prior art method as the mice are identical.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1,7,9,11,13,15-20,22,23,26,28-34,36,38,40,42-50 and 53-58 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,720,936 issued February 24, 1998 for reasons of record.

'936 teaches the an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 60-64 and claims 1,3 and 4). As the specification of '936 teaches mice having the same construct as the mice of the instantly claimed methods of screening, those mice of '936 would inherently develop the features and characteristics instantly claimed for the mouse of the screening assay.

Applicant argues that the transgenic mouse disclosed in 5,720,936 that produces expression products at the claimed levels, that is having a cDNA/genomic DNA APP construct, is specifically excluded from the claims. This argument is not persuasive. The only claims that exclude the cDNA/genomic DNA APP construct is excluded in claims 28 and 56. Applicant should refer to the amendment filed September 8, 1998. It noted that the claims in the appendix to the response of October 30, 2000 contain such a limitation. However, these are not the claims of record. If such a limitation enters the file, of course, the rejection will need to be reconsidered.

Applicant argues where a cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. Applicant argues that the rejection

provides not evidence that the claimed expression levels are necessarily present in the mice of 5,720,936 and no evidence that those of ordinary skill in the art would have recognized this. These arguments are not persuasive.

As stated above, the ordinary artisan would have expected the claimed mice and the mice of 5,720,936 to have the same phenotype as they are structurally the same. Applicant has not offered any reasoning or evidence that the mice which are structurally the same, that is having the same transgene construct -regulatory sequences and DNA sequence encoding APP, would not have the same phenotype. Again, newly recognized properties of an old product do not provide patentability of the old product. Further there is no requirement that extrinsic evidence be provided.

Claims 1,2,5-7,9,11,13,15-20,24-26,28,29,33,34,36,37,39,40,42-45,51-53 and 56-58 remain rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,604,102 issued February 18, 1997 for reasons of record.

'102 teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '102 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The specification clearly defines the NSE promoter as one promoter to be used in the instant claims

Applicant argues that when a reference is silent about an asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. Applicant argues that the rejection provides no evidence that the claimed expression was necessarily present in the mice of 5,604,102. These arguments are not persuasive.

For the same reasons provided in each of the above arguments to applicant's response, the mice of 5,604,102 are structurally the same, that is their transgene is contained within applicant's claims. If the mice contain the same transgene, then they would be expected by the ordinary artisan to express the

transgene products to the same level as those of the mice claimed. Further, there is no requirement for evidence of reaching the inherent expression level as the ordinary artisan would have so recognized the inherency. The evidence is that the transgenes are the same. Same transgenes are expected to behave the same.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-7,9,11,13,15-20,22,23,26,28-34,36,38,40,42-50 and 53-58 remain rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter for reasons of record.

U.S. Patent No. 5,720,936 issued February 24, 1998 teaches the an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 60-64 and claims 1,3 and 4). '936 is presently commonly assigned to Athena Neurosciences. The record indicates that at the time of invention '936 was assigned to TSI Corporation in paper no. 3 filed August 31, 1992.

Applicant argues that the only mouse in 5,720,936 that produces expression products at the claimed level has been specifically excluded. This argument is not persuasive.

Applicant argues that the transgenic mouse disclosed in 5,720,936 that produces expression products at the claimed levels, that is having a cDNA/genomic DNA APP construct, is specifically excluded from the claims. This argument is not persuasive. The only claims that exclude the cDNA/genomic DNA APP construct is excluded in claims 28 and 56. Applicant should refer to the amendment filed September 8, 1998. It noted that the claims in the appendix to the response of October 30, 2000 contain such a limitation. However, these are not the claims of record. If such a limitation enters the file, of course, the rejection will need to be reconsidered.

Applicant argues where a cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that

this would have been recognized by those of ordinary skill in the art. Applicant argues that the rejection provides not evidence that the claimed expression levels are necessarily present in the mice of 5,720,936 and no evidence that those of ordinary skill in the art would have recognized this. These arguments are not persuasive.

As stated above, the ordinary artisan would have expected the claimed mice and the mice of 5,720,936 to have the same phenotype as they are structurally the same. Applicant has not offered any reasoning or evidence that the mice which are structurally the same, that is having the same transgene construct -regulatory sequences and DNA sequence encoding APP, would not have the same phenotype. Again, newly recognized properties of an old product do not provide patentability of the old product. Further there is no requirement that extrinsic evidence be provided.

Claims 1,2,5-7,9,11,13,15-20,24-26,29,33,34,36,38,40,42-45,51-53 and 56-58 remain rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter for reasons of record.

U.S. Patent No. 5,604,102 issued February 18, 1997 teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '102 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The specification clearly defines the NSE promoter as one promoter to be used in the instant claims.

Applicant argues that when a reference is silent about an asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. Applicant argues that the rejection provides no evidence that the claimed expression was necessarily present in the mice of 5,604,102. These arguments are not persuasive.

For the same reasons provided in each of the above arguments to applicant's response, the mice of 5,604,102 are structurally the same, that is their transgene is contained within applicant's claims. If the mice contain the same transgene, then they would be expected by the ordinary artisan to express the transgene products to the same level as those of the mice claimed. Further, there is no requirement for evidence of reaching the inherent expression level as the ordinary artisan would have so recognized the inherency. The evidence is that the transgenes are the same. Same transgenes are expected to behave the same.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments that U.S. Patent 5,387,742 does not teach or suggest the production of amyloid plaques that stain with Congo red in the brains of transgenic mice expressing a APP transgene is persuasive to overcome the rejection made in the previous office action.

Applicant's arguments that U.S. Patent 5,387,742 issued February 7, 1995 in view of Sasahara et al (1991) Cell 64, 217-227 in view of any of Mullen et al (1992) Nature Genetics 1, 345-347, Chartier-Harlin et al (1991) Nature 353, 844-846 and Hendriks et al (1992) Nature Genetics 1, 218-221 does not teach or suggest the production of amyloid plaques that stain with Congo red in the brains of transgenic mice expressing a APP transgene is persuasive to overcome the rejection made in the previous office action.

Claims 1-20,22,23,26,29-50,53,54,,57 and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Games et al (1995) Nature 373, 523-527 for reasons of record. Games et al teach, and thereby offers motivation, that the transgenic mice disclosed therein can be used to determine the effectiveness of compounds that lower Aβ production in vitro in an in vivo assay (page 527, col. 1, parag. 1, lines 8-13). The transgenic mice are taught to express a transgene encoding APP770 V717F operatively

linked to the PDGFβ promoter and to develop brain morphologies associated with Alzheimer's Disease: dense plaques, GFAP, neuritic processes, synaptophysin and MAP-2 (page 524, col. 2, parag. 1, lines 10-12 and page 526, col. 1, lines 19-21; col. 1-2, bridg, sent. and col. 2, lines 11-14).

Applicant argues that the construct taught by Games et al is excluded from the instant claims, and that Games does not teach any other constructs that produce transgenic mice having the same phenotype as that of the mice of the method claims. These arguments are not persuasive.

The only claims of record that disclaim the Games et al mouse is claim 28 and 56. The preliminary amendment filed September 8, 1998 only contains the disclaimer in claims 28 and 56. The claims of record encompass the transgenic mice of Games et al.

Claims 1-7,9,11,13,15-20,22,23,26,29-34,36,38,40,42-50,53,54,57 and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,811,633 for reasons of record.

'633 teaches a transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 7, line 65 to col. 8, line 8, line 32 to col. 9, line 8 and claims 1 and 3-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 43-48 and claims 1 and 6). The mice are taught to be an assay model for determining compounds for the treatment of Alzheimer's Disease (col. 15, lines 31-40).

Applicant argues that there is no suggestion or motivation in 5,811,633 to even try to produce mice having the claimed expression levels. Applicant argues that the claimed expression levels was not known until applicant's discovery of it. Applicant argues that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the patent. These arguments are not persuasive.

If the transgene construct of the mice in 5,811,633 is encompassed by applicant's claims, then those mice will reach the claimed expression levels. Applicant needs to provide clear rationale as to why this would not be the case. This embodiment of the claims is sufficient to render the claim in its entirety

obvious. Once applicant removes this embodiment from the claim, then the obviousness rejection would probably fall. Further, applicant is attempting to patent a known product. Apparently applicant believes that because they have found a previously unrecognized phenotype of the mice in 5,811,633, they are entitled to a patent to the old product. However, this is not true. A product and its properties can not be separated. An unrecognized feature, property or phenotype to an old product does not render the old product patentable for another time. The extension of monopoly to the old product would continue.

Claims 1,2,5-7,9,11,13,15-20,24-26,28-30,33,34,36,38,40,42-48,51-53 and 56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,612,486 for reasons of record.

'486 teaches a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 13, line 56-66; col. 24, lines 45-53 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '486 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The mice of '486 are taught to be useful in screening assays to determine pharmaceuticals for treating Alzheimer's Disease (col. 23, lines 44-50).The specification clearly defines the NSE promoter as one promoter to be used in the instant claims.

Applicant argues that there is no suggestion or motivation in 5,612,486 to even try to produce mice having the claimed expression levels. Applicant argues that the claimed expression levels was not known until applicant's discovery of it. Applicant argues that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the patent. These arguments are not persuasive.

If the transgene construct of the mice in 5,612,486 is encompassed by applicant's claims, then those mice will reach the claimed expression levels. Applicant needs to provide clear rationale as to why this would not be the case. This embodiment of the claims is sufficient to render the claim in its entirety obvious. Once applicant removes this embodiment from the claim, then the obviousness rejection would probably fall. Further, applicant is attempting to patent a known product. Apparently applicant believes that because they have found a previously unrecognized phenotype of the mice in 5,612,486, they are

entitled to a patent to the old product. However, this is not true. A product and its properties can not be separated. An unrecognized feature, property or phenotype to an old product does not render the old product patentable for another time. The extension of monopoly to the old product would continue.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20,22-26 and 28-58 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for testing or screening compounds for an effect on an Alzheimer's disease marker wherein a compound of interest is administered to transgenic mice whose somatic and germ cells contain a nucleic acid construct comprising a PDGFβ promoter operatively linked to a cDNA-genomic DNA hybrid sequence, wherein said hybrid sequence contains a cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein a genomic APP DNA sequence consisting of exon 6 and an amount of the adjacent downstream intron sufficient for splicing, the KI and OX-2 coding region and an amount of each of their upstream and downstream introns sufficient for splicing, and exon 9 and an amount of the adjacent upstream intron sufficient for splicing is substituted into the corresponding region of the cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein expression of the transgene results in the claimed phenotype at 2-4 months of age, and where the Alzheimer disease marker is an increase or decrease in a protein selected from the group consisting of synaptophysin, GFAP, phosphorylated tau, phosphorylated neurofilaments, MAP-2, Aβtot, Aβ1-42, Aβ1-40, FLAPP + APPα and APPβ; where the Alzheimer's disease marker is a behavior selected from the group consisting of working or reference behavior, locomotor activity, emotional reactivity and object recognition; and where the Alzheimer's disease marker is a histopathology selected from the group consisting of compact plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density and neutrophil abnormalities, does not reasonably provide enablement for the nucleic acid

constructs specifically claimed and the breadth of mammals for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues that the claims contain an expression level phenotype, and that because of this phenotype, mice which do not achieve this expression level are excluded from the claims. Applicant argues that the claims that only constructs that achieve this expression level are included in the claim language. Applicant argues that prior art animals that do not achieve the claimed phenotype are excluded from the claims. Applicant argues that there is no evidence for, and is evidence against, the prior art sought high levels of expression of Aβ-related expression products. These arguments are not persuasive.

The issue at hand is whether or not applicant's claims are predictable without an undue about of experimentation, The citation of prior mice that fall with the scope of applicant's claim, but did not reach the level of expression claimed is clear evidence that applicant's claim is unpredictable. While the issue of the prior art seeking or not seeking high levels of expression can be debated, the one issue that can not be debated is the desire and need of the prior art to have in its possession an animal that sufficiently mimicked Alzheimer's Disease that the mouse could be used as an assay system for testing therapeutic protocols. The fact that applicant achieved high levels of expression and made at least one type of mouse that develops some hallmark features, such a Congo red staining plaques, of Alzheimer's Disease, so not in and of itself mean that the breadth of applicant's claims are predictable without undue experimentation. This is especially noteworthy in view of the failures of the prior art to produce a transgenic mouse expressing an APP that had Congo red staining plaques in it's brain. Applicant has been given a scope rejection in keeping with the disclosed mouse, but where the production of the mouse is reproducible in a predictable manner without undue experimentation on the part of the inventor.

Applicant argues that the cited portions of Lannfelt et al are speculating on possible reasons as to why the prior art attempts to produce a transgenic mouse model for Alzheimer's Disease. Applicant argues that there is not evidence that the speculation is accurate. Applicant argues that Lannfelt et al does not address the difficulty of achieving high levels of expression. Applicant argues that Lannfelt et al only notes

that expression levels of the APP transgene were low in the failed animals. These arguments are not persuasive.

Lannfelt et al is published review article, summarizing the state of Alzheimer's Disease transgenesis, and the problems encountered by investigators in the area. Lannfelt et al sets forth a serious of reasons as to why the art has been so unsuccessful in their attempts to express an APP transgene in the brain of a mouse such that the mouse develops sufficient symptoms that it can serve as an Alzheimer's Disease model. The reasoning presented by Lannfelt et al is worthy for establishing the unpredictable nature of producing an Alzheimer's Disease mouse. Remember, it isn't that applicant has shown nothing, but the breadth of claim scope due applicant given a disclosure of one transgene producing, as applicant refers, a high level of expression that leads to a reasonable transgenic mouse mimicking some features of Alzheimer's Disease. If Lannfelt et al states that expression is a problem, and applicant teaches one means of establishing such expression, then unpredictability can be established for other transgenes. In this regard, the speculation set forth in Lannfelt et al is reliable on its face as it is the learned opinion of those in the art. If high expression of the APP transgene is the key to the claimed Alzheimer's mouse, then the specification must provided guidance as to achieving the high level of expression. Applicant has only taught one, for which a scope broader than the actual disclosed transgene, has been given. As taught by Lannfelt et al, the art did not teach a means to achieve a useful Alzheimer's mouse. Thus, as the art could not be relied upon by the skilled artisan for guidance to high expression of the APP transgene and the producing of a useful Alzheimer's mouse, the specification must provide such teachings, and this specification does so for only one embodiment of the claims.

Applicant argues that Sirinathsinghji et al supports their argument that a high level of expression is an important determinant of obtaining useful phenotypes in mice transgenic for APP constructs. Applicant argues that Sirinathsinghji et al discusses three mice useful for Alzheimer's Disease studies, those taught in Games et al, Hsiao et al, and Sommer et al. Applicant argues that Sirinathsinghji et al also teach that it is clear that mutations associated with Alzheimer's disease all lead to increased levels of A/β

and that results with mice overexpression A/β is consistent with, and confirms, the importance of A/β production in the development of Alzheimer's Disease. These arguments are not persuasive.

The Games et al mouse will not be discussed as it is the disclosed mouse, and the Games et al mouse falls squarely within the scope of claims given above.

Both the Hsiao et al mouse and the Sommers et al mice use promoters not disclosed by applicant. The Hsiao et al mouse uses a prion promoter to direct expression of a mutant APP coding sequence, and the Sommers et al mouse uses a Thy1 promoter to direct expression of a mutant APP coding sequence. As applicant has argued, expression level is Germane to the instant invention, and thus the promoters used in the transgenic mice is Germane. Thus, the promoters that cause a high level of expression would necessarily need to be disclosed for the art of Hsiao et al or Sommers et al to be persuasive. Further, as each of Hsiao et al and Sommers et al, and is reiterated by Sirinathsinghji et al, the APP transgene associated with such high expression would need to be a mutant APP. A reading of Sirinathsinghji et al shows that the exact phenotypes of the Games et al mouse, the Hsiao et al mouse and the Sommers et al mouse are not identical (pages 48-49). Thus, the ability to achieve the instant claims state specific protein production levels at particular ages of the mice is not apparent from Sirinathsinghji et al as there is no specific discussion for any of the mouse of Games et al, the mouse of Hsiao et al or Sommers et al. Thus, it is not known how closely these mice match the specifically claimed phenotypes claimed. The issue isn't really about high expression, but the predictability of obtaining a mouse with the claimed phenotypes without an undue amount of experimentation on the part of the skill artisan. High expression is one way to achieve such. Applicant has provided one means. Others in the art have provided other means. However, as applicant has not disclosed the other artisan's means, that art does not support applicant's allegations of enablement as a critical inventive feature is missing from the instant disclosure. Applicant has not provided any guidance as to other promoters that would permit a mouse of the same phenotype as that claimed to be produced.

Applicant argues that Mucke et al teaches that the levels of Aβ in young mice is an important determinant of obtaining a useful phenotype in mice transgenic for APP constructs. Applicant argues that

Mucke et al shows that mice expression Aβ at high levels can be produced reliably and repeatedly. Applicant argues that Mucke et al also support enablement because they show that prior transgenic animals with similar constructs but poor phenotypes are not evidence that the present high expression levels are precluded for a particular constructs. In particular, applicant argues, that Mucke et al obtained different transgenic mice using the same construct by exhibiting a variety of expression levels. Applicant argues that Mucke et al provides evidence that mice as claimed can be produced without the need for undue experimentation. These arguments are not persuasive.

Mucke et al only teaches the use of transgene constructs identical or similar to the transgene construct of the scope rejection in the production of transgenic mice expressing APP in their brains. Mucke et al states "the PDGF promoter was used to direct neuronal expression of alternatively spliced minigenes encoding hAPP695, hAPP751 and hAPP770 as described previously (Games et al 1995; Rockenstein, 1995)", page 4051, col. 2, parag. 5, parag. 6, lines 1-4). These constructs are the cDNA/genomic DNA hybrid of the scope limitation above. Thus there is no evidence in Mucke et al that prior art unsuccessful constructs that yielded poor phenotypes are evidence to precluded for specific constructs. Mucke et al never showed constructs that did not work before to work because of higher expression. Mucke et al only manipulated the Games et al construct, that had been shown to produce mice with a "robust" Alzheimer's disease related phenotype, and which is in the scope rejection above, although in broader form. In fact the evidence presented in figure 3 supports the examiner's limitation to an APP comprising a mutation at amino acid position 717. Mice having a wild type APP transgene produced very little Aβ, but those with mutations would be considered high producers of Aβ and Aβ-related peptides. Further, Mucke et al states that in mice with a wild type transgene, amyloid plaques were not detected (page 4055, col. 1, parag. 1, lines 1-5). Thus, Mucke et al teaches that in using APP cDNA/genomic DNA minigenes, as disclosed in the instant specification and Games et al, wild type APP does not lead to amyloid plaques production. Thus the wild type APP scope of the claims is not enable. Mucke et al teaches that at a minimum the APP cDNA/genomic DNA construct needs to contain a mutation at amino acid position 717. This is included in the above scope rejection. Mucke et al, in each of their constructs, used the PDGF promoter, which is also

included in the scope rejection. Thus, Mucke et al supports the above scope rejection as it adds nothing to the disclosure such that applicant's allegations that they are entitled to a broader scope are supported. The only expression level shown in Mucke et al to associate with a "robust" phenotype associated with Alzheimer's Disease is Aβ production level, and each such construct is within the above scope rejection. It is noted in figure 1B that mice expressing a wild type APP minigene, had high levels of APP production but did not produce amyloid plaques.

Applicant argues that they have taught those of skill in the art wishing to obtain murine models of Alzheimer's disease to focus on obtaining transgenic mice having the required level of expression of Aβ-related expression products and reasonably expect that they will have useful phenotypes. Applicant argues that the instant situation is like the situation in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) where production of the claimed monoclonal antibodies in only 2.3% of attempts to make such antibodies was acceptable experimentation. Applicant argues that In Wands the court was influenced by the fact that in the relevant art such efforts and rates of success were normal and expected. Applicant argues that it is normal and acceptable in the art of transgenesis that several attempts be made to produce a transgenic mouse expressing a desired transgene. These arguments are not persuasive.

The issue here is not like that of Wands. While the degree of experimentation is high in the production of transgenic non-human animals, the art also teaches the unpredictable nature of the art. While applicant only discussed Lannfelt et al, several other references were also cited to establish the unpredictable nature of the claimed invention. In deed the findings of Higgins et al, as cited in the previous office action, is confirmed by Mucke et al in that mice expression a wild type APP transgene do not produce amyloid plaques in their brains. For this scope of the instant claims, there are now on the record two avenues, with two transgene constructs, one of which the constructed used by Mucke et al, was shown to cause plaque formation in mice expressing an APP transgene having an amino acid substitution at APP717. Further, others, such as Greenberg et al, taught that APP transgene constructs falling within the scope of applicant's claims did not produce mice that developed amyloid plaques in their brain. The specification provides no guidance, with the exception of the scope rejection subject matter,

how to take the wild type APP transgene constructs of Mucke et al and Higgins et al, or the wild type and mutant transgene constructs of Greenberg et al, each of which failed at plaque formation, and make these constructs expression sufficient Aβ to produce amyloid plaques in the brains of transgenic mice. This is the missing guidance, this is what the specification does not teach or provide guidance for and this is where the specification is deficient. It is not enough to state that a certain phenotype is required, and where that phenotype has been shown not to occur in transgenic mice that fall within the scope of applicant's claims, and state obtaining such a phenotype is predictable without undue experimentation. The level of guidance in the specification is small given the failures taught in the art and the unpredictable nature of the invention also taught in the art at the time of filing. Further, enablement requires reproducibility. The only reproducibility provided by applicant is in the form of Mucke et al which uses transgene constructs that fall within the scope of invention given above. There is no evidence anywhere on the record that fall outside of the scope limitation and within the guidance provided in the specification.

Applicant argues that they examiner makes arguments regarding the phenotype of the claimed animals and the correlation of these phenotypes to Alzheimer's disease. Applicant argues that the phenotypes recited in the claims make the mice useful for Alzheimer's Disease studies. This argument is not persuasive.

The issue in the previous office action is not about the phenotypes of the mice, but how the phenotype of the mouse is displayed in the cells from the mouse. The claims of record are to an assay using transgenic mice or cells from the transgenic mice, but the claims never states what the cells do to make them an assay system. It is not seen how the cells will be useful for the majority of markers claimed. Protein markers are fine, but behavioral markers and brain morphological makers are not fine.

Applicant argues that markers claimed are disclosed in the specification and they believe each of these markers is associated with Alzheimer's disease. Applicant argues that for a model for such a devastating disease that the art can not wait for certainty in an assay and model before identifying therapeutics. These arguments are not persuasive.

The argument is that nothing can be found in the relevant art that each of the markers claimed are recognized as markers for Alzheimer's. In such a devastating disease, one would not want a researcher to spend any time on a marker that was not clearly involved in the disease. There is no showing in the art for the extensive list of markers claimed.

Claims 8,10,12,14,35,37,39 and 41 are free of the prior art. At the time of filing the cited prior art did not teach or suggest a method for testing compounds for an effect on an Alzheimer's Disease maker using a transgenic mouse and testing the markers claimed. The art at the time of filing did not teach the association of the markers claimed in 8,10,12,14,35,37,39 and 41 as being associated with Alzheimer's disease.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Karen Hauda, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
January 27, 2001